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EXPLORING METHYLATION SIGNATURES FOR HIGH DE NOVO RECURRENCE RISK IN HEPATOCELLULAR CARCINOMA

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Background : Hepatocellular carcinoma (HCC) exhibits high de novo recurrence rates post-resection. Current post-surgery recurrence prediction methods are limited, emphasizing the need for reliable biomarkers to assess recurrence risk. We aimed to develop methylation-based markers for classifying HCC patients and predicting their risk of de novo recurrence post-surgery.

Methods : In this retrospective cohort study, we analyzed data from HCC patients who underwent surgical resection in Korea, excluding those with recurrence within one-year post-surgery. Using the Infinium Methylation EPIC array on 140 samples in the discovery cohort, we classified patients into low- and high-risk groups based on methylation profiles. Distinctive markers were identified through random forest analysis. These markers were validated in The Cancer Genome Atlas (TCGA; n=217), Validation Cohort 1 (n=63) and experimental validation using a methylation-sensitive high-resolution melting (MS-HRM) assay in Validation Cohort 1 and Validation Cohort 2 (n=63).

Results : The low-risk recurrence group (Methylation Group 1; MG1) showed a methylation average of 0.73 (95% CI, 0.69-0.77) with a 23.5% recurrence rate, while the high-risk group (MG2) had an average of 0.17 (95% CI, 0.14-0.20) with a 44.1% recurrence rate ($p<0.03$). Validation confirmed the applicability of methylation markers across diverse populations, showing high accuracy in predicting the probability of HCC recurrence risk (AUC 96.8%). The MS-HRM assay confirmed its effectiveness in predicting de novo recurrence with 95.5% sensitivity, 89.7% specificity, and 92.2% accuracy.

Conclusions : Methylation markers effectively classified HCC patients by de novo recurrence risk, enhancing prediction accuracy and potentially offering personalized management strategies.

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